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10/560,098	04/28/2006	Taro Miyazaki	14875-154US1 C1-A0304P-US	1173
26161	7590	10/23/2007	EXAMINER	
FISH & RICHARDSON PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			BRISTOL, LYNN ANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/560,098

Applicant(s)

MIYAZAKI ET AL.

Examiner

Lynn Bristol

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 3, 4 and 9-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-8 and 22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 4/28/06; 3/29/07; 5/16/07.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

1. Claims 1-22 are all the pending claims for this application.
2. The Preliminary Amendment to the specification of 12/9/05 has been considered and entered.
3. New claim 22 was added in the Reply of 8/10/07.

Election/Restrictions

4. Applicant's election without traverse of Group I (Claims 1, 2, 5-8 and 22) in the reply filed on 8/10/07 is acknowledged. Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
5. Claims 3, 4 and 9-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/10/07.
6. Claims 1, 2, 5-8 and 22 are all the pending claims under examination.

Information Disclosure Statement

7. The U.S., international and foreign patent references and the non-patent literature references cited in the IDS' of 4/28/06; 3/29/07; and 5/16/07 have been considered and entered.

Specification

8. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Applicants are requested to insert the section "Brief Description of the Figures" (on pp. 22-23 of the specification) between the "Brief Summary of the Invention" and "Detailed Description of the Invention".

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Claim Objections

9. Claims 5-8 and 22 are objected to for the following reasons:

Claims 5-8 depend from non-elected claims 3 and 4 and should be amended to change their dependency to only Claims 1 and 2;

Claim 22 is objected to for apparent typographical errors: "expressions" should be spelled "expression."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2, 5-8 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1 and 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Alternatively, Claims 1 and 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are:

1) the step(s) for inhibiting the contact between the L and H chains. Does this involves a chemical reactant or does the physical structure of the first and second light

chains with respect to the first and second heavy chains of the antibody confer this aspect of the method.

2) the elements describing the physical organization of the antibody in order to achieve the intended effect of inhibiting contacts. How are the light and heavy chain elements structurally related?

b) Claims 5-8 recite the limitation "the first and the second H chain" and "the first and the second L chain" in Claim 5. There is insufficient antecedent basis for this limitation in the claim or in Claim 2 from which the claims depend.

c) Claim 7 recites the limitation "the first pairs or the second pairs". There is insufficient antecedent basis for this limitation in the claim.

d) Claims 7 and 8 are indefinite for the phrase "the antibody is unlikely to be formed from a combination of just the first pairs or the second pairs" because it is not clear how the antibody formation should actually occur if random pairs of antibodies would not necessarily be expected to combine under the method.

e) Claims 2, 5-8 and 22 are indefinite for the recitation "a first pair and a second pair of the antibody" in Claim 2 because it is not clear if the two pairs should be of the same antibody or the first and second pair should be a different antibody.

f) Claim 22 is indefinite as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the vector *encoding* the first H chain and first L chain under the control of a first inducible promoter and the vector encoding the second H chain and second L chain under the control of a second inducible promoter. It is not clear how

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each vector, each pair of H and L chains and the expression regulator are physically or structurally related.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1, 2, 5-8 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al., J. Immunol. Methods 248:7-15 (2001); cited in the IDS of 4/28/06) in view of Peipp et al., Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) and Shalaby et al., J. Exp. Med. 175:217-225 (1992); cited in the IDS of 4/28/06).

Claim 1 is rejected for indefiniteness as discussed supra, but for purposes of examination and to advance prosecution, the claim is interpreted as being drawn to a method for preparing a bi-specific antibody. Claim 2 is drawn to a method for producing

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an antibody comprising expressing a first and second pair of the antibody at different times. Claims 5-8 which depend from Claims 1 and 2 are interpreted as being drawn to the method where the amino acid sequences of the first and second H chains are different and the amino acid sequences of the first and second light chains are different (Claim 5), where the antibody of Claim 5 is bi-specific (Claim 6), where the antibody of Claim 6 is unlikely to be formed from a combination of just the first or the second pairs (Claim 7), where the antibody of Claim 7 is prepared using knobs-into-holes technique (Claim 8), and where the method comprises using a vector to induce expression of a first H chain and a first L chain from a first expression regulator and a vector to induce expression of a second H chain and a second L chain from a second expression regulator.

The claimed method for producing a bi-specific antibody was prima facie obvious at the time of the invention over Carter, Peipp and Shalaby.

Carter describes a process for producing a bispecific antibody having an Fc region, wherein the H chain and L chain which constitute a first set have a antigen recognition site and the H chain and L chain which constitute a second pair have another antigen recognition site and are expressed simultaneously, and the formation of the first pair and the second pair and the bonding of said first pair and second pair by knobs-in-hole are carried out simultaneously. Carter also describe antibodies produced having antigen recognition sites comprising the H chain which makes up the first pair and the L chain which makes up the second pair. Carter does not disclose expressing

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the first and second antibodies at different times but Peipp and Shalaby rectify this deficiency.

Peipp and Shalaby describe the V region of the H chain and L chain which constitute a particular antigen recognition site and the V region of H chain and L chain which make up another antigen recognition site are separately expressed in E coli and that the respective H chain and L chain are bonded in advance and their respective antigen recognition sites formed, after which the two antigen recognition sites are chemically bonded, thereby efficiently producing the target bispecific antibody.

One skilled in the art would have been motivated at the time of the invention to have made the process for producing a bispecific antibody having an Fc region and been reasonable assured of success based on the disclosures of Carter, Peipp and Shalaby. The method of Carter could readily have been modified by one of skill in the art based on Pipp and Shalaby disclosing that the separate expression of an H chain and L chain which constitute a first pair having a particular antigen recognition site and an H chain and L chain which constitute a second pair having another antigen recognition site, and to bond their respective H chain and L chains in advance, forming a first pair and a second pair having antigen recognition site, and subsequently bonding the first pair and second pair via knob-in-hole, in order to prevent the production of antibodies having antigen recognition sites comprising undesirable sets and to efficiently produce the target bispecific antibody. Further one of skill in the art could introduce an optimum expression regulating factor and carry out the expression of the H chain and L chain which constitute the first pair, and an H chain and L chain which

constitute the second pair in separate cells at different times. Because Carter taught the general method for producing bispecific antibodies and Peipp and Shalaby describe different techniques for expressing different antibody pairs from different vectors could be accomplished in *E. coli*, one of ordinary skill in the art could have readily introduced the vector system of Peipp or Shalaby into the method of Carter and would be reasonably assured that the expressed antibody pairs would have formed a bispecific antibody.

12. Claims 1, 2, 5-8 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ridgeway et al., Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) in view of Peipp et al., Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) and Shalaby et al., J. Exp. Med. 175:217-225 (1992); cited in the IDS of 4/28/06).

The interpretation of Claims 1, 2, 5-8 and 22 is discussed supra.

The claimed method for producing a bi-specific antibody was prima facie obvious at the time of the invention over Ridgeway, Peipp and Shalaby.

Ridgeway describes a process for producing a bispecific antibody having an Fc region, wherein the H chain and L chain which constitute a first set have a antigen recognition site and the H chain and L chain which constitute a second pair have another antigen recognition site and are expressed simultaneously, and the formation of the first pair and the second pair and the bonding of said first pair and second pair by knobs-in-hole are carried out simultaneously. Ridgeway also describe antibodies

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produced having antigen recognition sites comprising the H chain which makes up the first pair and the L chain which makes up the second pair. Ridgeway does not disclose expressing the first and second antibodies at different times but Peipp and Shalaby rectify this deficiency.

Peipp and Shalaby are discussed supra.

One skilled in the art would have been motivated at the time of the invention to have made the process for producing a bispecific antibody having an Fc region and been reasonable assured of success based on the disclosures of Ridgeway, Peipp and Shalaby. The method of Ridgeway could readily have been modified by one of skill in the art based on Peipp and Shalaby disclosing that the separate expression of an H chain and L chain which constitute a first pair having a particular antigen recognition site and an H chain and L chain which constitute a second pair having another antigen recognition site, and to bond their respective H chain and L chains in advance, forming a first pair and a second pair having antigen recognition site, and subsequently bonding the first pair and second pair via knob-in-hole, in order to prevent the production of antibodies having antigen recognition sites comprising undesirable sets and to efficiently produce the target bispecific antibody. Further one of skill in the art could introduce an optimum expression regulating factor and carry out the expression of the H chain and L chain which constitute the first pair, and an H chain and L chain which constitute the second pair in separate cells at different times. Because Ridgeway taught the general method for producing bispecific antibodies and Peipp and Shalaby describe different techniques for expressing different antibody pairs from different vectors could

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be accomplished in *E. coli*, one of ordinary skill in the art could have readily introduced the vector system of Peipp or Shalaby into the method of Ridgeway and would be reasonably assured that the expressed antibody pairs would have formed a bispecific antibody.

Conclusion


13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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